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16955DIV2CIP NON-ACIDIC CYCLOPENTANE HEPTANOIC ACID, 2-CYCLOALKYL OR ARYLALKYL DERIVATIVES AS THERAPEUTIC AGENTS

5 <u>Crossreference to Related Applications</u>

This patent application is a continuation-in-part of U.S. Patent Application Serial No. 08/371,339, filed on January 11, 1995 which is a continuation of U.S. Patent Application Serial No. 08/154,244 which was filed on November 18, 1993, which is a divisional of U.S. Patent Application Serial No. 07/948,056, filed on September 21, 1992, now U.S. Patent No. 5,352,708 issued on October 4, 1994, all of which are hereby incorporated by reference.

15 **Background of the Invention**

1. Field of the Invention

The present invention provides cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compounds, which may be substituted in the 1-position with amino, amido, ether or ester groups, e.g., a 1-OH cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compound. The cyclopentane heptanoic acid, 2-(cycloalkyl or arylalkyl) compounds of the present invention are potent ocular hypotensives, and are particularly suitable for the management of glaucoma. Moreover, the cyclopentane heptanoic, 2-(cycloalkyl or arylalkyl) compounds of this invention are smooth muscle relaxants with broad application in systemic hypertensive and pulmonary diseases; smooth muscle relaxants with application in gastrointestinal disease, reproduction, fertility, incontinence, shock, etc.

2. Description of the Related Art

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as postsurgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupillary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not

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indicated, topical b-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Prostaglandins were earlier regarded as potent ocular hypertensives; however, evidence accumulated in the last two decades shows that some prostaglandins are highly effective ocular hypotensive agents and are ideally suited for the long-term medical management of glaucoma. (See, for example, Starr, M.S. Exp. Eye Res. 1971, 11, pp. 170-177; Bito, L. Z. Biological Protection with Prostaglandins Cohen, M. M., ed., Boca Raton, Fla, CRC Press Inc., 1985, pp. 231-252; and Bito, L. Z., Applied Pharmacology in the Medical Treatment of Glaucomas Drance, S. M. and Neufeld, A. H. eds., New York, Grune & Stratton, 1984, pp. 477-505). Such prostaglandins include PGF_{2a}, PGF_{1a}, PGE₂, and certain lipid-soluble esters, such as C_1 to C_5 alkyl esters, e.g. 1-isopropyl ester, of such compounds.

In the United States Patent No. 4,599,353 certain prostaglandins, in particular PGE_2 and PGF_{2a} and the C_1 to C_5 alkyl esters of the latter compound, were reported to possess ocular hypotensive activity and were recommended for use in glaucoma management.

Although the precise mechanism is not yet known, recent experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et al., Invest. Ophthalmol. Vis. Sci. 28(suppl), 284 (1987)].

The isopropyl ester of PGF2a has been shown to have significantly greater hypotensive potency than the parent compound, which was attributed to its more effective penetration through the cornea. In 1987 this compound was described as "the most potent ocular hypotensive agent ever reported." [See, for example, Bito, L. Z., Arch. Ophthalmol. 105, 1036 (1987), and Siebold et al., Prodrug 5, 3 (1989)].

Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular PGF2a and its prodrugs, e.g. its 1-isopropyl ester, in humans. The clinical potential of prostaglandins in the management of conditions associated with

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18	data	transfer	request,	said da	ta transf	er hub	further	controlling
19	said	source po	rt and sa	aid dest	ination p	ort to		

in response to a data transfer request, query said destination port to determine if said destination port is capable of receiving data of a predetermined size+,

if said destination port is not capable of receiving data of said predetermined size, waiting by not reading data of said predetermined size from said source port corresponding to said data transfer request and not transferring data to said destination port until said destination port is capable of receiving data, and

if said destination port is capable of receiving data of said predetermined size, reading data of said predetermined size from said source port and transferring said read data to said destination port.

1 8. (Currently Amended) The data transfer controller of claim 2 7, wherein:

each port includes at least one write reservation station for storing data prior to transfer to said corresponding external memory/device;

said data transfer hub further controlling said destination port to

determine whether any write reservation station of said destination port has not been allocated for receipt of data, and

if at least one write reservation is not allocated for receipt of data, determining said destination port can receive data and allocating a write reservation station for receipt of data, and

15 <u>transfer said read data to said allocated write</u> 16 <u>reservation station of said destination port.</u>

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1	9.	(Original)	The	data	transfer	controller	of	claim	8,
2	wherein:								

said data transfer hub further controlling said destination port to

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9 10 transfer data from a write reservation station to said corresponding external memory/device at a data transfer rate of said external memory/device, and

disallocating said write reservation station upon transfer of data from said write reservation station to said external memory/device.

1 10. (Currently Amended) The data transfer controller of claim 2 8, wherein:

each of said plurality of hubs ports further includes an didentifier register corresponding to each write reservation station; and

said data transfer hub further controlling said destination port to

allocate a write reservation station by writing identifier data in said corresponding identifier register, and store said read data in a write reservation station having a corresponding identifier stored in said identifier register corresponding to said write reservation station.

1 11. (Currently Amended) The data transfer controller of claim $2 \pm \frac{7}{2}$, wherein:

said data transfer controller hub further capable of servicing

4 a second transfer request between said source port and a second

5 destination port while waiting until said destination port is

6 capable of receiving data of

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determining if a second data transfer request between
said source port and a second destination port is pending,
if a second data transfer request is pending

querying said second destination port to determine if said second destination port is capable of receiving data of said predetermined size,

if said second destination port is not capable of receiving data, waiting by not reading data of said predetermined size from said source port corresponding to said second data transfer request until said second destination port is capable of receiving data, and

if said second destination port is capable of receiving data, reading data of said predetermined size from said source port and transferring said read data to said second destination port.

12. (Canceled)

13. (Currently Amended) A data processing system comprising: a plurality of data processors, each data processor capable of

generating a data transfer request;

a request queue controller connected to said plurality of data processors, said request queue controller receiving, prioritizing and dispatching data transfer requests, each data transfer request specifying a data source, a data destination and a data quantity to be transferred;

a data transfer hub connected to request queue controller effecting dispatched data transfer requests;

a plurality of ports, each of said plurality of ports having an interior interface connected to said data transfer hub identically configured for each port and an exterior interface configured for an external memory/device expected to be connected

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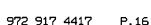
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to said port, said interior interface and said exterior interface 15 16 operatively connected for data transfer therebetween; and

said data transfer hub controlling data transfer from a source port corresponding to said data source to a destination port corresponding to said data destination in a quantity corresponding to said data quantity to be transferred of a currently executing data transfer request, said data transfer hub further controlling said source port and said destination port to

in response to a data transfer request, query said destination port to determine if said destination port is capable of receiving data of a predetermined size+,

if said destination port is not capable of receiving data of said predetermined size, waiting by not reading data of said predetermined size from said source port corresponding to said data transfer request and not transferring data to said destination port until said destination port is capable of receiving data, and

if said destination port is capable of receiving data of said predetermined size, reading data of said predetermined size from said source port and transferring said read data to said destination port.

1 (Currently Amended) The data processing system of claim 2 13, wherein:

each port includes at least one write reservation station for storing data prior to transfer to said corresponding external memory/device;

said data transfer hub further controlling said destination 6 port to 7

determine whether any write reservation station of said destination port has not been allocated for receipt of data, and

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11	if at least one write reservation is not allocated for
12	receipt of data, determining said destination port can receive
13	data and allocating a write reservation station for receipt of
L 4	data <u>, and</u>

transfer said read data to said allocated write reservation station of said destination port.

(Original) The data processing system of claim 14, 15. wherein:

3 said data transfer hub further controlling said destination 4 port to

> transfer data from a write reservation station to said corresponding external memory/device at a data transfer rate of said external memory/device, and

> disallocate said write reservation station upon transfer of data from said write reservation station to said external memory/device.

1 (Original) The data processing system of claim 14, 16. 2 wherein:

3 each of said plurality of hubs further includes an identifier register corresponding to each write reservation station; and

5 said data transfer hub further controlling said destination 6 port to

7 allocate a write reservation station by writing identifier data in said corresponding identifier register, and 8 9 store said read data in a write reservation station having a corresponding identifier stored in said identifier 10 11 register corresponding to said write reservation station.

1 (Currently Amended) The data processing system of claim 2 13, wherein:

3 said data transfer controller hub further capable of servicing a second transfer request between said source port and a second 4 destination port while waiting until said destination port is 5 6 capable of receiving data of 7 determining if a second data transfer request between 8 said source port and a second destination port is pending, if a second data transfer request is pending 10 querying said second destination port to determine if said second destination port is capable of receiving 11 12 data of said predetermined size, 13 if said second destination port is not capable of 14 receiving data, waiting by not reading data of said 15 16

predetermined size from said source port corresponding to said second data transfer request until said second destination port is capable of receiving data, and if said second destination port is capable of

receiving data, reading data of said predetermined size from said source port and transferring said read data to said second destination port.

(Canceled)

(Currently Amended) The data processing system of claim 19. 13, further comprising:

said plurality of ports includes an internal port master;

a data transfer bus connected to said internal port master and each of said data processors, said data transfer bus transferring data between said plurality of data processors and said data transfer hub via said internal port master;

a system memory connected to a predetermined one of said plurality of ports; and



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wherein each of said data processors includes an instruction cache connected to said data transfer bus for temporarily storing program instructions controlling said data processor, said data processor generating a data transfer request to said request queue controller for program instruction cache fill from said system memory to said instruction cache upon a read access miss to said instruction cache.



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14 15 20. (Currently Amended) The data processing system of claim 13, further comprising:

said plurality of ports includes an internal port master;

a data transfer bus connected to said internal port master and each of said data processors, said data transfer bus transferring data between said plurality of data processors and said data transfer hub via said internal port master;

a system memory connected to a predetermined one of said plurality of ports; and

wherein each of said data processors includes a data cache connected to said data transfer bus for temporarily storing data employed by said data processor, said data processor generating a data transfer request to said request queue controller for data cache fill from said system memory to said data cache upon a read access miss to said data cache.

1 21. (Currently Amended) The data processing system of claim 2 13, further comprising:

3 said plurality of ports includes an internal port master;

4 <u>a data transfer bus connected to said internal port master and</u>
5 <u>each of said data processors, said data transfer bus transferring</u>

6 data between said plurality of data processors and said data

7 <u>transfer hub via said internal port master;</u>



a system memory connected to a predetermined one of said plurality of ports; and

wherein each of said data processors includes a data cache connected to said data transfer bus for temporarily storing data employed by said data processor, said data processor generating a data transfer request to said request queue controller for data writeback from said data cache to said system memory upon a write miss to said data cache.

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22. (Currently Amended) The data processing system of claim 13, further comprising:

said plurality of ports includes an internal port master;

a data transfer bus connected to said internal port master and each of said data processors, said data transfer bus transferring data between said plurality of data processors and said data transfer hub via said internal port master;

a system memory connected to a predetermined one of said plurality of ports; and

wherein each of said data processors includes a data cache connected to said data transfer bus for temporarily storing data employed by said data processor, said data processor generating a data transfer request to said request queue controller for write data allocation from said system memory to said data cache upon a write miss to said data cache.

23. (Currently Amended) The data processing system of claim 2 13, further comprising:

said plurality of ports includes an internal port master;

a data transfer bus connected to said internal port master and each of said data processors, said data transfer bus transferring data between said plurality of data processors and said data

7 <u>transfer hub via said internal port master;</u>

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a system memory connected to a predetermined one of said plurality of ports; and

wherein each of said data processors includes a data cache connected to said data transfer bus for temporarily storing data employed by said data processor, said data processor generating a data transfer request to said request queue controller for data writeback from said data cache to said system memory upon eviction of dirty data from said data cache.

1 24. (Original) The data processing system of claim 13, 2 wherein:

said plurality of data processors, said request queue controller, said data transfer hub and said plurality of ports are disposed on a single integrated circuit.

25. (Currently Amended) The data processing system of claim 2 13, further comprising:

a data memory having a data transfer bandwidth on the same order as a data transfer bandwidth of said data transfer hub;

5 <u>a second</u> <u>an internal memory</u> port connected to said data 6 transfer hub and said data memory; and

said data transfer hub further controlling said source port and said destination port to not query said second internal memory port to determine if said destination port is capable of receiving data of a predetermined size if said second internal memory port is a destination port of a data transfer request.